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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/560,491	06/09/2006	Michiyo Yanase	YAMAP0997US	9721

43076 7590 02/26/2009

MARK D. SARALINO (GENERAL)
RENNER, OTTO, BOISSELLE & SKLAR, LLP
1621 EUCLID AVENUE, NINETEENTH FLOOR
CLEVELAND, OH 44115-2191

EXAMINER	
SAIDHA, TEKCHAND	

ART UNIT	PAPER NUMBER
1652	

MAIL DATE	DELIVERY MODE
02/26/2009	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/560,491	YANASE ET AL.	
	Examiner	Art Unit	
	Tekchand Saidha	1652	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *17 November 2008*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,3-5,7,8,16-19 and 34* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,3-5,7,8,16-19 and 34* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *17 November 2008* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

FINAL REJECTION

1. Amendment and response filed 11/17/2008 is acknowledged. Claims 1, 3-5, 7-8, 16-19 & 34 are present and under consideration in this application.

2. Applicant's arguments filed 11/17/2008 have been fully considered but they are not deemed to be persuasive. The reasons are discussed following the rejection(s).

3. Any objection or rejection of record not expressly repeated in this Office Action has been overcome by Applicant's response and withdrawn.

4. **Claim Rejections - 35 USC § 112 (first paragraph)**

Enablement Rejection

Claims 1, 3-5, 7-8, 16-19 & 34 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for an isolated α-glucan phosphorylase having improved thermo stability, which is obtained by modifying a natural α-glucan phosphorylase, wherein the natural α-glucan phosphorylase is the sequence of SEQ ID NO: 2, and is obtained from a plant, and the α-glucan phosphorylase having improved thermo stability has an amino acid residue which is different from that of the natural α-glucan phosphorylase in a position corresponding to position 7 in a motif sequence 3L: R-I-V-K-F-I-T-D-V of SEQ ID NO: 47; and wherein enzyme activity of the α-glucan phosphorylase having improved thermo stability at 37°C, after heating in a 20 mM citrate buffer (pH 6.7) at 60°C for 10 minutes, is 20% or more of enzyme activity of the α-glucan phosphorylase having improved thermo stability at 37°C, before heating; does not reasonably provide enablement for the natural α-glucan phosphorylase (SEQ ID NO: 2) have one or several amino acids are deleted, substituted or added relative to an amino acid sequence of natural α-qlucan phosphorylase; wherein the enzyme activity of the α-qlucan phosphorylase having improved thermostability is equivalent or superior to the natural α-qlucan phosphorylase (claims 1 & 34); or wherein the natural α-glucan phosphorylase of SEQ ID NO: 2 to having *varying sequence homology* of at least 50% with respect to the to the sequences of SEQ ID NO: 2 (claim 3); or wherein the natural α-glucan phosphorylase of SEQ ID NO: 2 be hybridized under stringent conditions (claim 4). Claims 5, 7-8 & 16-19 depend on claim 1 and do not alter the scope claim 1 and are therefore included in this rejection. The specification does not enable any

person skilled in the art to which it pertains, or with which it is most nearly connected, to make the invention commensurate in scope with these claims.

The scope of the claims does not commensurate with the enablement provided by the disclosure with regard to the extremely large number of polypeptides broadly encompassed by the claims. Since the amino acid sequence of a protein determines its structural and functional properties, predictability of which changes can be tolerated in a protein's amino acid sequence and obtain the desired activity requires a knowledge of and guidance with regard to which amino acids in the protein's sequence, if any, are tolerant of modification and which are conserved (i.e. expectedly intolerant to modification), and detailed knowledge of the ways in which the proteins' structure relates to its function. However, in this case the disclosure is limited to the amino acid sequence of SEQ ID NO: 2. Other α-glucan phosphorylase sequences being disclosed in the specification.

While recombinant and mutagenesis techniques are known, it is not routine in the art to screen for multiple substitutions or multiple modifications, as encompassed by the instant claims, and the positions within a protein's sequence where amino acid modifications can be made with a reasonable expectation of success in obtaining the desired activity/utility are limited in any protein and the result of such modifications is unpredictable. In addition, one skilled in the art would expect any tolerance to modification for a given protein to diminish with each further and additional modification, e.g. multiple substitutions.

The specification does not support the broad scope of the claims which encompass all modifications of protein of SEQ ID NO: 2 to any extent or by 50%, because the specification does **not** establish: (A) regions of the protein structure which may be modified without effecting α-glucan phosphorylase (GP) activity; (B) the general tolerance of α-glucan phosphorylase enzyme to modification and extent of such tolerance; (C) a rational and predictable scheme for modifying any α-glucan phosphorylase enzyme residues with an expectation of obtaining the desired enzymatic or biological function and being thermostable and (D) the specification provides

insufficient guidance as to which of the essentially infinite possible choices is likely to be successful.

The instant specification, page 66, Table 4, provides a comparison of the sequence identities of various α-glucan phosphorylases. Further, the specification on pages 138 & 139 (Tables 8 & 9) provide examples of improved thermostabilities of mutant type-H GP. The specification or the prior art does not teach that the modification of the α-glucan phosphorylase from one source can enable the modification of another α-glucan phosphorylase from any source. Further, the prior art knowledge or the teachings of the instant specification do not establish specific regions, such as the catalytic domains of the α-glucan phosphorylase structure that can be or cannot be modified in order to improve the thermal stability of the α-glucan phosphorylases having no limit to the extent of modifications or having at least 50% modification in the sequence of SEQ ID NO: 2.

Thus, applicants have not provided sufficient guidance to enable one of ordinary skill in the art to make and use the claimed invention in a manner reasonably correlated with the scope of the claims. The scope of the claims must bear a reasonable correlation with the scope of enablement (In re Fisher, 166 USPQ 19 24 (CCPA 1970)). Without sufficient guidance, determination of exact nature of the α-glucan phosphorylase enzyme and the variants thereof is unpredictable and the experimentation left to those skilled in the art is improper, extensive and undue. See In re Wands 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988).

Applicants' Arguments:

Citing Exhibit 1 [Structure and properties of Thermus aquaticus a-glucan phosphorylase expressed in Escherichia coil T. Takaha, M. Yanase, H. Takata and S. Okada. J. Appl. Glycosci., (2001) 48, 71-78. Exhibit 1 describes the alignment score (%) between the amino acid sequences of glucan phosphorylase from various sources (e.g., bacterial, plant, and animals)] Applicants argue that glucan phosphorylase obtained from potato has a very low similarity (e.g., 9 and 10 %) to glucan phosphorylase obtained from bacteria (see Fig. 5 on page 77 of Exhibit 1). Moreover, the amino acid sequences of glucan phosphorylase derived from similar species having similar

properties have a relatively high similarity of 30-40%. As described in Table 4 on page 66 of the present specification, the percent identity (%) between the amino acid sequences of α-glucan phosphorylase derived from plants are very high and are **57% or more** with regard to 15 α-glucan phosphorylase shown in Table 4. Therefore, it would have been known to one of ordinary skill in the art, based on an active natural amino acid sequence, to obtain an active modified amino acid sequence by modifying one or several amino acid acids. Furthermore, the amino acid residue essential for glucan phosphorylase activity on the amino acid sequence of glucan phosphorylase was known in the art at the time of filing the present application. Applicants submit the attached Exhibit 2: Evolution of allosteric control in glycogen phosphorylase. John W Hudson, G. Brian Golding and Michael M Crerar. J. MoL Biol., (1993) 234, 700-721.

Applicants arguments are considered but not found to be persuasive because while the percent identity (%) between the amino acid sequences of α-glucan phosphorylase derived from plants are very high and are **57% or more** with regard to 15 α-glucan phosphorylase shown in Table 4, the data does not provide guidance to modification of specific amino acids to any extent or at least 50% with regard to the sequence of SEQ ID NO: 2. It is not clear from Applicants' arguments – which of the amino acid residues were considered essential for activity with respect to the sequence of SEQ ID NO: 2. Exhibits I and II do not clarify specific regions of the sequence of SEQ ID NO: 2 which are commonly possessed by other glucan phosphorylases and are amenable to modifications in order to improve the thermostabilty of glucan phosphorylase(s). The rejection is therefore maintained.

5. Claims 1, 3-5, 7-8, 16-19 & 34 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The specification discloses the reduction to practice of one elected species and several non-elected species within the claimed genus; specifically, the protein having the amino acid sequence of SEQ ID NO: 2. There are no drawings or structural

formulas disclosed of any other protein having the function of α-glucan phosphorylase enzyme, other than the sequence homology comparison in Figure 1 (A-I). There is no teaching in the specification regarding the 50% or more of the structure of SEQ ID NO: 2 that can be varied while retaining the ability of the protein to function as a α-glucan phosphorylase enzyme and be thermostable. Further, there is no art recognized correlation between any structure (other than SEQ ID NO: 2) and the α-glucan phosphorylase enzyme activity. Consequently there is no information about which amino acids can vary from SEQ ID NO: 2 in the claimed genus and still retain the catalytic activity.

Although the disclosure of SEQ ID NO: 2 combined with the knowledge would put one in possession of proteins that are at least 50% identical to SEQ ID NO: 2, the level of skill and knowledge in the art is such that one of ordinary skill would not be able to identify without further testing which of those proteins having at least 50% identity to SEQ ID NO: 2 (if any) and having the activity of α-glucan phosphorylase enzyme. Based on the lack of knowledge and predictability in the art, those of ordinary skill in the art would not conclude that Applicant was in possession of the claimed genus of proteins based on the disclosure of several naturally occurring proteins having α-glucan phosphorylase enzyme activities without guidance to specific modifications.

6. No claim is allowed.

7. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1, 3-5, 7-8, 16-19 & 34 are rejected under 35 U.S.C. 102(b) as being anticipated by Accession No. Q9LKJ3 (2000). Accession No. Q9LKJ3 is an α-glucan phosphorylase, is at least 50% identical to the sequence of SEQ ID NO: 2 and wherein position 7 in motif "RIVKFITDV" is 'N'. See the sequence search alignment between Accession Number Q9LKJ3 and Applicants' SEQ ID NO: 2, presented below.

The α-glucan phosphorylase of Accession No. Q9LKJ3 is considered no difference than the broadly claimed variant of SEQ ID NO: 2 having no limitation to the extent of modifications (claim 1 & 34) and/or at least 50% identical to SEQ ID NO: 2 (claim 3). The α-glucan phosphorylase of Accession No. Q9LKJ3 also inherently possess improved thermostability and other limitations recited in the claims. The reference anticipates the claims.

<u>Sequence search alignment between Accession Number Q9LKJ3 and Applicants' SEQ ID NO: 2</u>

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RESULT 13
PHSH_WHEAT
ID   PHSH_WHEAT              Reviewed;         832 AA.
AC   Q9LKJ3;
DT   11-JUL-2001, integrated into UniProtKB/Swiss-Prot.
DT   01-OCT-2000, sequence version 1.
DT   24-JUL-2007, entry version 39.
DE   Alpha-glucan phosphorylase, H isozyme (EC 2.4.1.1) (Starch
DE   phosphorylase H).
OS   Triticum aestivum (Wheat).
OC   Eukaryota; Viridiplantae; Streptophyta; Embryophyta; Tracheophyta;
OC   Spermatophyta; Magnoliophyta; Liliopsida; Poales; Poaceae; BEP clade;
OC   Pooideae; Triticeae; Triticum.
OX   NCBI_TaxID=4565;
RN   [1]
RP   NUCLEOTIDE SEQUENCE [MRNA].
RC   STRAIN=cv. Star; TISSUE=Leaf;
RA   Schupp N.T., Ziegler P., Huebsch S.D.;
RT   "Full length clone of a cytosolic wheat leaf starch phosphorylase.";
RL   Submitted (JUN-2000) to the EMBL/GenBank/DDBJ databases.
CC   -!- FUNCTION: Phosphorylase is an important allosteric enzyme in
CC       carbohydrate metabolism. Enzymes from different sources differ in
CC       their regulatory mechanisms and in their natural substrates.
CC       However, all known phosphorylases share catalytic and structural
CC       properties (By similarity).
CC   -!- CATALYTIC ACTIVITY: (1,4-alpha-D-glucosyl)(n) + phosphate = (1,4-
CC       alpha-D-glucosyl)(n-1) + alpha-D-glucose 1-phosphate.
CC   -!- COFACTOR: Pyridoxal phosphate.
CC   -!- SUBCELLULAR LOCATION: Cytoplasm (By similarity).
CC   -!- SIMILARITY: Belongs to the glycogen phosphorylase family.
CC   ----------------------------------------------------------------------

  Query Match             55.5%;  Score 2806;  DB 1;  Length 832;
  Best Local Similarity   58.7%;  Pred. No. 1.3e-165;
  Matches  527;  Conservative  127;  Mismatches  164;  Indels   80;  Gaps    6;

Qy         70 SSFAPDAASITSSIKYHAEFTPVFSPERFELPKAFFATAQSVRDSLLINWNATYDIYEKL 129
              |  : | ::|  :| |||:::| |||  |   :||:|||:|||| ||  || ||  : | 
Db         12 SPASEDPSAIAGNISYHAQYSPHFSPLAFGPEQAFYATAESVRDHLLQRWNDTYLHFHKT 71

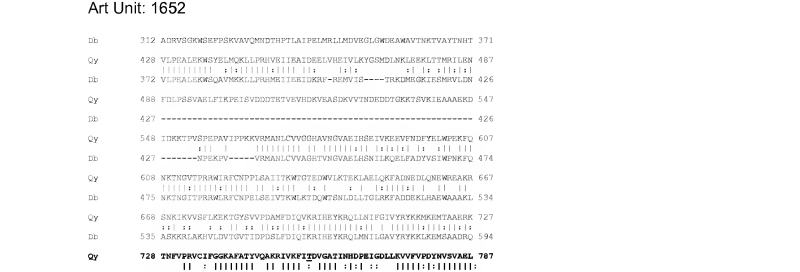
Qy        130 NMKQAYYLSMEFLQGRALLNAIGNLELTGAFAEALKNLGHNLENVASQEPDAALGNGGLG 189
              : || ||||||:|||||| ||:||| :|||:|:|||  |: || :| || ||||||||||
Db         72 DPKQTYYLSMEYLQGRALTNAVGNLAITGAYADALKKFGYELEAIAGQERDAALGNGGLG 131

Qy        190 RLASCFLDSLATLNYPAWGYGLRYKYGLFKQRITKDGQEEVAEDWLEIGSPWEVVRNDVS 249
              |||||||||:|||| |:|||||||:|||||||||| |:||||:|||||:  ||||:||:|| 
Db        132 RLASCFLDSMATLNLPSWGYGLRYRYGLFKQRIAKEGQEEIAEDWLDKFSPWEIVRHDVV 191

Qy        250 YPIKFYGKVSTGSDGKRYWIGGEDIKAVAYDVPIPGYKTRTTISLRLWSTQVPSADFDLS 309
              |||:|:| |    |||| ||| : |:|||||||||||:  ||||||     : ||:| 
Db        192 YPIRFFGHVEISPDGKRKWAGGEVLNALAYDVPIPGYKTKNAISLRLWDATATAEDFNLF 251

Qy        310 AFNAGEHTKACEAQANAEKICYILYPGDESEEGKILRLKQQYTLCSASLQDIISRFERRS 369
               || |::  | :  : |::|| :||||| :||||:|||||||| |||||||||| ||: | 
Db        252 QFNDGQYESAAQLHSRAQQICAVLYPGDATEEGKLLRLKQQYFLCSASLQDIIFRFKERK 311

Qy        370 GDRI--KWEEFPEKVAVQMNDTHPTLCIPELMRILIDLKGLNWNEAWNITQRTVAYTNHT 427
               ||:  || ||| ||||||||||||| ||||||:|:|::|| |:||| :| :||||||||
```



8. During a telephone interview with the Applicants' representative, Heidi A Boehlefeld, on February 23, 2009, allowable subject matters were discussed and Applicants were invited to amend the claims to place them in condition for allowance. However, the discussion did not result in an agreement being reached hence this Office Action.

In claim 1 the following language was proposed: Replace claim 1 lines 16-22 with the following:

... "wherein the α-glucan phosphorylase having improved thermostability has an amino acid sequence which is at least 95% identical to the sequence of SEQ ID NO: 2 (residues 1-916).

It was also proposed to amend claim 34 similarly and cancel claim 3.

It was also proposed to amend claim 4, line 5, by replacing '**an** amino acid sequence' with '**the** amino acid sequence'.

9 Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP

§ 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

10. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Tekchand Saidha whose telephone number is (571) 272 0940. The examiner can normally be reached on 8.30 am - 5.00 pm. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Nashaat Nashed can be reached on (571) 272 0934. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Tekchand Saidha/
Primary Examiner, Art Unit 1652
Recombinant Enzymes, 02A65 Remsen Bld.
400 Dulany Street, Alexandria, VA 22314
Telephone: (571) 272-0940
February 23, 2009